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CAPILLARY PERMEABILITY IN TRAUMATIC SHOCK

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One of us [Engel, 1940] has recently worked out a method for determining directly the permeability of the capillaries in a given region. This method appeared suitable for reinvestigation of the problem of increased permeability of capillaries in 'traumatic shock'. We have therefore examined whether, after crushing a limb, there occurs an increase in the filtration through the capillaries either confined to the traumatized region and its immediate neighbourhood or generalized throughout the body.

In traumatic shock a great quantity of plasma is assumed to escape from the blood vessels owing to their increased permeability. Evidence for this loss of plasma is of a twofold nature: the haemoconcentration found in man as well as in experimental animals during traumatic shock and the increase in weight of a traumatized limb. Both findings, however, are open to a different interpretation. Haemoconcentration may be due to escape of fluid constituents of blood, but it may also occur as a result of mobilization of blood corpuscles from the blood reservoirs, especially the spleen and the bone marrow. This possibility has not always been excluded as a cause of the haemoconcentration. The increase in weight of a traumatized limb, found by Blalock [1930] has been contested by some [Moon, 1938] but confirmed by others [Phemister, 1928; Harkins, 1941]. It results from loss into the crushed limb out of the vessels, of plasma as well as blood, in amounts sufficient to account for death. It is not possible to determine to what extent the increase in weight is due to escape of whole blood from broken or torn vessels or to escape of fluid through the capillary walls. Beard & Blalock [1931], by centrifuging crushed tissue in order to separate the extravascular fluid, attempted to show that the oedema fluid of a crushed limb has a similar composition as serum. This method, however, does not differentiate between the plasma of the extra- and intravascular blood in the tissue and the extravascular oedema fluid. Both will appear in the supernatant fluid on centrifugation. There is thus no direct evidence of an increased capillary permeability in shock.

Neither is there any clear evidence if the accepted increased permeability of the capillaries is generalized or confined to the traumatized area. Blalock [1940], in criticizing the toxaemic theory, concludes that 'there is no convincing proof that local injury in itself produces general damage to all capillaries and tissues'.

Methods

The experiments were carried out on cats, with the exception of one experiment which was performed on a rabbit. The animals were anaesthetized by intramuscular injection of 0·5 c.c./kg. of nembutal (for veterinary purposes) about 1 hr. before the actual preparation was started. A cannula was tied into the carotid artery for recording the arterial blood pressure. Chlorazol fast pink (0·1 g./kg.) was injected intravenously as an anticoagulant. At different times, about hourly, the haemoglobin concentration of blood samples taken from the otherwise unused jugular vein was determined with the Sicca haemoglobinometer.

Determination of rate of filtration through the capillaries. A dye was injected into the jugular vein at a constant rate throughout the experiment, while the two knee joints were perfused with Ringer solution. The dye circulating in the blood will appear in the perfusate of the knee joints after it has passed the capillary endothelium, the synovial membrane and the fine layer of tissue connecting the two. We measured the filtration through this composite membrane, which will be referred to as the articular barrier. A diagrammatic representation of the barrier and its relation to the perfusion is given in Fig. 1 B. The apparatus for the perfusion of the knee joints and the infusion of the dye is illustrated in Fig. 1 A. It consisted of two identical record syringes of 10 c.c., and a third syringe of 20 c.c., which were mounted firmly side by side, and the pistons of which were pushed forward simultaneously by a metal wheel (*w*) so as to empty the three syringes at an identical steady rate. The propelling of the wheel was effected by a motor as described elsewhere [Engel, 1941]. The 20 c.c. syringe, connected by rubber tubing (*a*) to a cannula tied into the jugular vein, contained a dye solution, usually of 1 % acid fuchsin, which was infused at a rate of about 0·7 c.c./min. Each 10 c.c. syringe was connected by rubber tubing (b, b_1) with a needle inserted into the left and right knee joint respectively, medial to the patella. These syringes were filled with Ringer solution which was warmed in its passage along the rubber tube by an electrically heated jacket (not indicated in the figure). A needle was inserted into each knee-joint cavity lateral to the patella allowing the fluid to flow out of the cavity (small arrows in Fig. 1), which in a cat held between 2 and 4 c.c. of perfusate. Care was taken to avoid bleeding in order to keep the articular barrier intact. Only perfusates free from blood were considered satisfactory and, at the end of each experiment, it was ascertained whether the tips of the needles had been in the joint cavities. The perfusates were collected separately

from each knee joint every 20–30 min. and the dye content was determined colorimetrically. The syringes were emptied in about half an hour.

The dye concentration in the blood was estimated every hour. 0·5 c.c. blood was removed from the jugular vein not used for the dye infusion, diluted to 1/200 and centrifuged. The supernatant fluid was compared colorimetrically with a standard dye solution after addition of a few drops of acetic acid to regenerate the acid fuchsin (a procedure followed also with the perfusates). The solution was the same as used for the perfusates from the knee joints (1/400,000). (The dye concentration was expressed in millimetres, as read on the colorimeter.) In any one experiment the same quantity of the perfusate

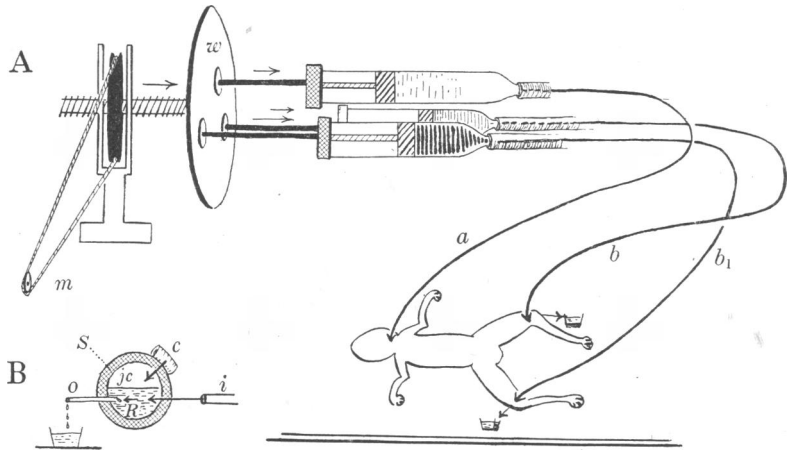

Fig. 1. A. Arrangement for knee perfusion. *w*, wheel pushing the three pistons; *a*, tubing connected with jugular vein; *b*–b_1, tubing connected with the two knee joints. The two small arrows represent the cannulae emptying the perfused joints. (For details see text.) B. Showing the dialysing process from one capillary (*c*), supplying the synovial membrane (*S*), into the joint cavity (*jc*) which is perfused with Ringer solution (*R*). *i*, inflow; *o*, outflow; *m*, motor.

—10–40 mm. high column as read on the colorimeter—was compared with the standard solution, recorded again in millimetres, and charted so in the curves. The figures obtained are relative values, but the absolute quantities can easily be calculated from them.

In addition to measuring the dye excretion into the knee joints we have measured the temperature of the quadriceps muscles with two copper-constantan thermo-couples, each inserted into a serum needle, by the usual thermo-electric method [for details see Engel, 1941].

Crushing the limbs. In one series of experiments one of the hind legs, including the foot, was traumatized before or during the perfusion of the knee joints, the other leg serving as a control. At the end of the experiment the two hind legs were weighed after dividing the pelvis in the midline according to the technique of Blalock [1930]. When the crushing was performed several hours

before the perfusion of the knees it was done under a short ether anaesthesia. The trauma consisted of 80–100 hammer blows to the soft parts of the extremities, usually to the parts distal to the knee joints, but in a few experiments the region of the thigh was traumatized either alone or in addition. In another series of experiments both forelegs and feet were similarly traumatized during the perfusion of the knee joints, and the dye excretion of both was compared before and after crushing. In most experiments the tibia, fibula and the tarsal bones of the hammered limbs were also fractured. Care was taken not to break the skin, but some slight bleeding could not always be avoided.

Results

In animals without trauma the dye excretion from the perfused knee joints was practically identical on both sides and increased gradually in the course of the experiment, with the gradual accumulation of dye in the blood. The dye excretion was approximately proportional to the blood dye concentration, variations being due to various factors which were out of control (*p*H of body tissue, renal and liver excretion of dye, etc.). The temperature of the two quadriceps muscles did not differ by more than 0·1–1·0° C. It usually decreased considerably due to the slow general cooling caused by the nembutal.

Crushing one hind leg

This was followed by considerable swelling of the limb which at the end of the experiment, lasting about 6 hr., weighed 50–130 g. more (average 90 g. or 3% of the body weight) than the uncrushed limb of the other side. The crushing caused first a very marked increase and later a decrease of dye excretion from the perfused knee joint of the crushed leg in comparison to the excretion from the control side. The increased excretion started a few minutes after the crushing and was detectable in the sample of perfusate collected during the first 20 min. after the trauma. In twelve experiments (eleven cats, one rabbit) the increased dye excretion, when at its maximum, was 2–7 times (average 3·5 times) greater than the excretion from the control leg. This increase lasted from 1 to 3 hr. and was followed by decreased excretion, continuing usually to the end of the experiment. Only when the animal died during the perfusion did the excretion rise again to some degree shortly before death, probably on account of a general anoxia.

In those experiments in which no blood pressure was recorded the dye excretion before the trauma was observed for a longer period. The excretion increased gradually on both sides with the increased dye concentration in the blood. The trauma was often followed by a drop in the excretion of the non-traumatized side. This drop amounted sometimes to over 25%, while there was a concurrent increase of dye excretion of 100% on the traumatized side.

A typical experiment illustrating the initial increase and later decrease of dye excretion after trauma is given in Fig. 2*C*. The immediate increase was followed

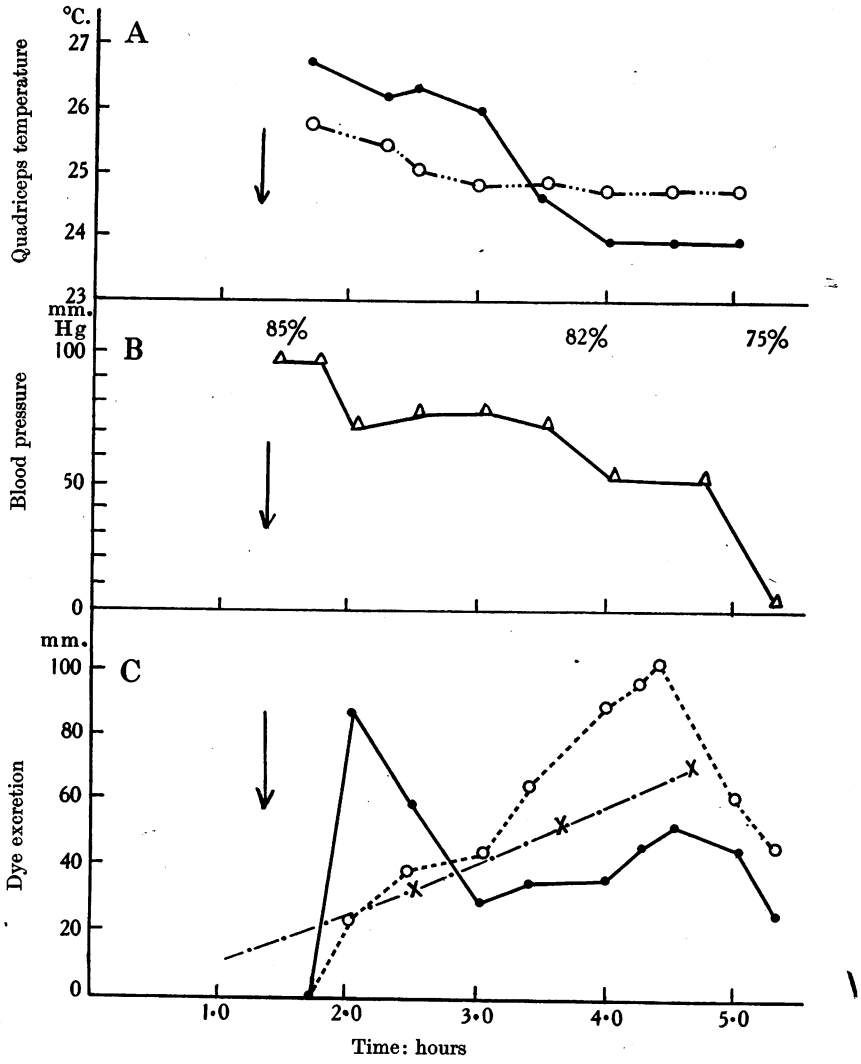

Fig. 2. Effect of crushing right hind leg on muscle temperature (*A*), blood pressure (*B*), and dye excretion (*C*). In *A* and *C* continuous line, right crushed; dotted line, left hind leg. Interrupted line in *C*, dye concentration of blood (reduced to 1/200). The arrows indicate time of crushing. Abscissae: time in hours. The figures on top of *B* are haemoglobin concentration of venous blood.

after 2 hr. by a decrease below the level of the control side despite the rise in blood-dye concentration. The blood pressure in this experiment is given at *B*, the figures on top of the tracing are haemoglobin concentrations of the blood

at the times indicated. In this and many other experiments, the blood pressure, although falling gradually, was maintained on a relatively high level for a considerable time before the final collapse occurred with heart failure, preceded by a period of Cheyne Stokes's respiration. No absolute haemoconcentration has been observed in this or any of the other experiments, the haemoglobin percentage actually fell below the pretraumatic level. This absence of haemoconcentration may have resulted from the severity of the trauma and the consequent considerable loss of whole blood from the torn vessels as witnessed by the large muscle tears and haematomata at post-mortems. Moreover, the blood was diluted throughout the experiment by the intravenous infusion of fuchsin solution at the rate of 40 c.c./hr. leading to hydraemia. Under the given conditions haemoglobin percentages of 50–75 after 4–5 hr. infusion must in fact be considered as relatively high values.

There was no correlation between the degree of dye excretion and the gravity of the shock condition as indicated by the arterial blood pressure or the swelling of the crushed limb. This was not to be expected. Compensatory mechanisms, which may maintain the arterial blood pressure for a considerable time, render it difficult to assess the condition of shock at a given moment of the experiment. Neither is the swelling of the crushed limb a true indication for increased permeation of plasma, since it results partly and to a varying degree from blood extravasates.

In only one experiment was the initial increased dye excretion after crushing absent. The procedure in this experiment differed from that adopted in the other twelve by the fact that the crushing was not limited to the parts distal to the knee joint but included the thigh. Post-mortem, a large haematoma was found round the femoral vessels probably compressing them. Some of the blood vessels to and from the knee joint were probably severed and nervous lesions could not be excluded. These facts may be responsible for the absence of the initial increased dye excretion.

In six experiments a colloidal dye, trypan blue, was infused in a 1% concentration into the jugular vein simultaneously with the non-colloidal acid fuchsin. This dye, which does not pass the articular barrier under normal conditions [Engel, 1940], also failed to appear in the perfusate from the traumatized side, though it has the greatest degree of dispersity in the series of those dyes which do not pass the barrier of the normal knee joint. This may be due to the fact that the trypan blue is too toxic to be given in a sufficiently strong concentration or that the dye is taken up too readily by the reticulocytes.

Measurements of temperature of the quadriceps muscles showed no definite correlation between increased dye excretion and changes in temperature. Although in the majority of the experiments the temperature of the traumatized side was 0·3–1·0° C. higher than the control side the ratio was reversed in three. In one of these the temperature of the traumatized side started to rise

at the late stage of the experiment when the dye excretion had decreased and the temperature became even higher than that of the control side. In the experiment of Fig. 2 the temperature of both muscles throughout the experiment is given in the tracings at *A*.

Late effects

The late decrease in the excretion of the dye from the crushed leg was studied separately in twelve cats by crushing the leg 3–23 hr. before the perfusion of the knee joints was started. In ten of these the crushing was inflicted upon the calf and foot. Perfusion was started in eight, after 3–4½ hr., in two, after 23 hr. In only two experiments in which the perfusion was started 3 and 4 hr. respectively after the trauma was there an increased dye excretion from the joint of the traumatized limb. This increase was small (15 and 60% respectively) and lasted for 1 and 2 hr. only. Later on, excretion from the traumatized leg diminished and became considerably smaller than from the control side. In the other eight experiments the dye excretion was much smaller on the traumatized side from the beginning to the end of the perfusion (3–4 hr.). The difference amounted to between 100 and 600%. The increased dye excretion from the traumatized side observed in the two experiments must be regarded as a delay of the transition of the first phase into the second, indicating that the decreased excretion does not always begin exactly 3 hr. after the trauma but may be delayed for another hour or two. Six hours, however, was the maximum time limit within which increased dye excretion has been observed from the traumatized side. A typical experiment illustrating the late decrease in dye excretion from a traumatized limb is given in Fig. 3. Perfusion was started 23 hr. after crushing of the left leg, at a time when the animal was in a weakened general condition and when the left leg was considerably swollen. At the end of the experiment it was found to weigh 130 g. more than the right leg. In this experiment the early dye excretion from the control knee fell at about 3.30 p.m. simultaneously with the appearance of signs of heart failure. Shortly before death the excretion rose again, an effect repeatedly observed in a dying animal.

In two experiments the crushing was inflicted on the thigh and perfusion started 3½ hr. later. In the one experiment dye excretion from the traumatized side was 20% greater throughout the whole 2½ hr. perfusion than from the control leg. In the other experiment this condition was observed in the first half-hour, afterwards the excretion from the traumatized side decreased considerably and became much smaller than that from the normal side.

In five experiments trypan blue was infused simultaneously with the acid fuchsin. It did not appear in any sample of perfusate of either knee joint.

The temperature of the quadriceps muscle of the traumatized side was in most experiments 0·2–1·5° C. higher despite the much smaller dye excretion from the knee joint of this side.

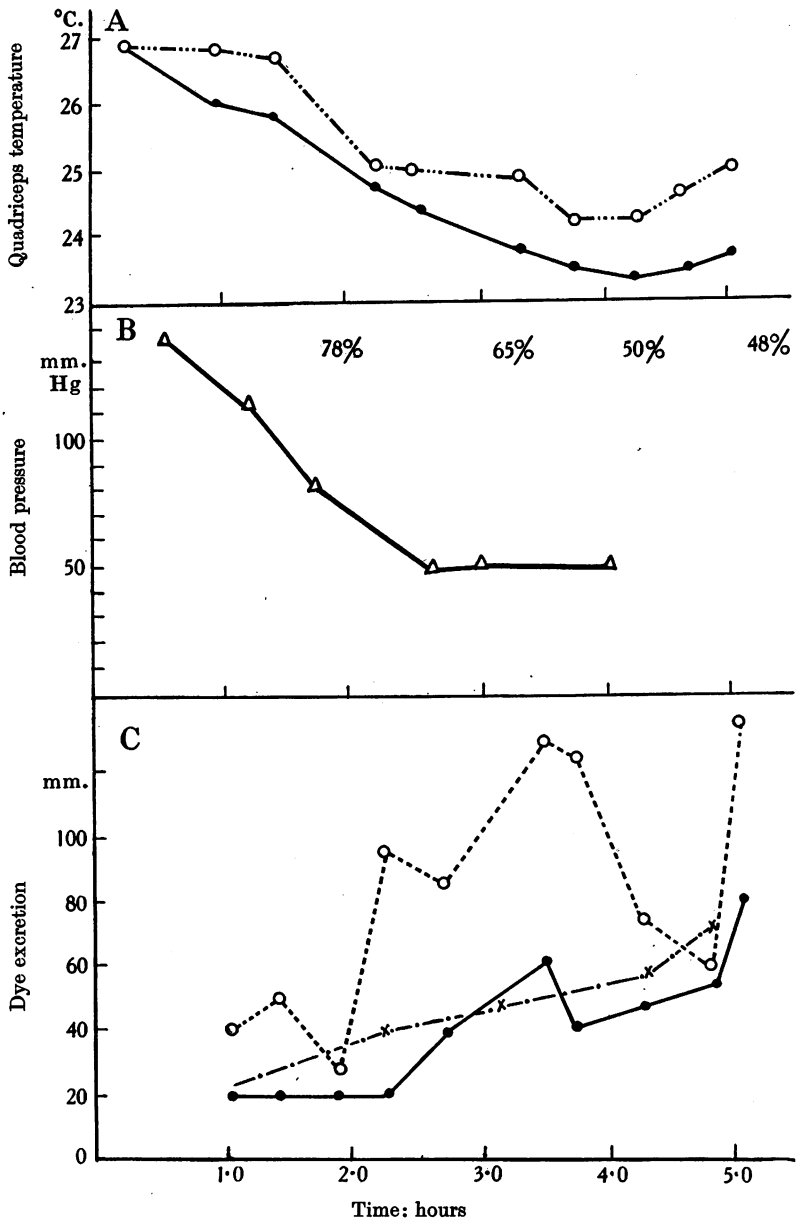

Fig. 3. Decreased dye excretion of traumatized right leg (continuous line) as compared with the excretion of the left control leg (dotted line), 23 hr. after trauma. Symbols as in Fig. 2.

Crushing both forelegs

Shortly after crushing both forelegs the dye excretion drops considerably from both knee joints in contrast to the rise in those experiments in which the trauma was inflicted near the perfusion area. A typical experiment is illustrated in Fig. 4. The dye concentration in this case fell from 24 to 5 mm. on the right and from 36 to 4·5 mm. on the left side to rise later to 13 and 10 mm. respectively. Such a secondary rise usually occurred 2–3 hr. after the trauma;

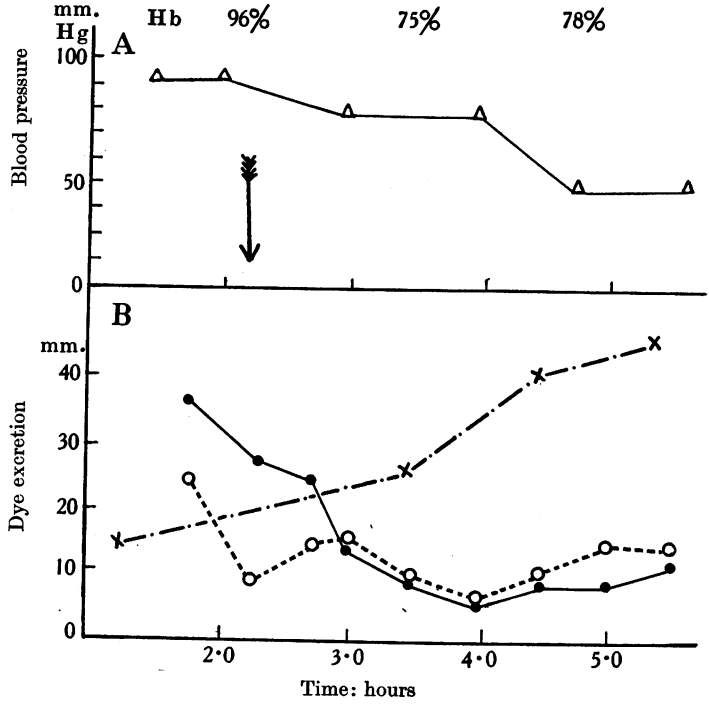

Fig. 4. Effect of crushing both forelegs on blood pressure (*A*), and dye excretion of both normal knee joints (*B*). Symbols as in Fig. 2.

sometimes the excretion reached the initial level or even exceeded it. However, in the meantime the dye concentration in the blood had also risen considerably. The secondary rise resembles the gradual increase in dye excretion which occurs in uninjured animals, perfused under otherwise similar conditions. It is due to the gradually increasing blood-dye level. This experiment was repeated eleven times with similar results. No immediate rise of dye excretion could be detected in the perfusates. Only one case deviated from this rule.

Discussion

The fact that the dye excretion from the perfused knee joint first increases and later decreases if a trauma is inflicted on the same limb below the knee, but shows an immediate diminution if the trauma is inflicted on a distant part of the body, is difficult to explain fully with the data at our disposal. The initial increase in dye excretion could not have been due to the rising concentration of dye in the blood, since this would have affected both the normal and the traumatized side. The lack of parallelism between dye excretion from the knee joint and change in temperature in the quadriceps muscle of the same leg makes it unlikely that the increased excretion resulted from a better blood supply to the traumatized leg, or that the subsequent decreased excretion had resulted from a reduced blood supply. The supposition was that the quadriceps muscle as the most intimately related to the knee joint has a very similar blood supply and will show a reaction similar to the joint. Though this assumption may be open to criticism, the fact that the temperature changes sometimes were in direct opposition to those to be expected if the dye excretion had been dependent upon the blood supply, supports the view that the observed changes in dye excretion which occurred when the trauma was inflicted on the same leg, are not, or at least not mainly, the outcome of changes in blood supply but of changes in the rate of filtration through the capillaries.

The immediate increase in rate of filtration through the capillaries in the neighbourhood of the trauma may be interpreted in different ways: one possibility, and in our opinion the most probable one, is that the capillary permeability in and around the area of trauma is temporarily increased. It is known [Landis, 1934] that the movement of fluids through the capillary wall is greatly influenced by the capillary blood pressure, the colloid osmotic pressure of the plasma proteins and the retention of proteins by the capillary wall. These factors were not measured in our experiments and therefore the theory of increased permeability as a cause of the increased dye filtration is not fully conclusive.

Another possible explanation is that the increased dye excretion is not a sign of an increase in general permeability of the capillaries in the knee joint, but that the acid dye may pass more readily through the membrane after the trauma because of a lowering of the *p*H.

It is unlikely that the late decrease in dye excretion which follows the period of increased dye excretion, when the trauma has been inflicted near the perfused region, is due to the same mechanism as that responsible for the immediate decrease in filtration through the capillaries, when the trauma has been inflicted at a distant part of the body, since the one condition develops when the other disappears. The immediate and late changes in permeability when the trauma is inflicted near the perfused joint closely resemble the conditions

developing in inflammation. With the same technique as used in our experiments it has been found [Engel, 1940] that the permeability in the knee joint, 24 hr. after an intra-articular injection of a 1% Lugol solution, was decreased as compared with the normal side, while according to Tani [1935], who used a different technique, dye excretion was increased during the first hours of inflammation caused by Lugol solution. In the area adjacent to the trauma a similar sterile inflammation appears to develop. This condition resembles or may be identical with what Eppinger, Faltitschek, Kaunitz & Popper [1935] described and demonstrated histologically as a serous inflammation. In the course of it the space between the synovial membrane and capillary endothelium would be imbued with fluid, probably plasma, and the double layer barrier changed into a more composite one which would offer greater resistance to the penetrating substances.

The immediate decrease in dye excretion from the knee joint when the trauma had been inflicted on the forelegs is most probably the result of a fall of dye concentration in the circulating blood, brought about by loss of dye into the traumatized tissue of the swollen forelegs. There is no fall of blood dye concentration in curve *B* in Fig. 4, possibly because it was missed between the two readings at 3.30 and 4.30 p.m. In other experiments the fall amounted to 30% and rose later again to the original level. A decreased dye concentration of the blood would lead to a fall of dye concentration in the articular perfusate without any change of the filtering capacity of the capillaries. This view is supported by the fact that this decrease in dye excretion lasts for a period of 3 hr., a time corresponding to the period of increased dye excretion into the traumatized tissue, as indicated by the experiments in which the trauma had been inflicted near the perfused knee joint.

Whatever the mechanisms responsible for the changes in dye excretion and in filtration through the capillaries may be, our results show that crushing tissue to such an extent that death ultimately ensues, does not cause an increase in filtration through the capillaries throughout the body, but only in the neighbourhood of the traumatized tissue. Thus our results support the view expressed by Moon [1938] that 'the main factor which is most probably responsible for the continued low blood pressure after injuries is not a general increase in capillary permeability with loss of fluid all over the body, but a loss of blood plasma through the walls of the damaged capillaries'. The conception of Short [1913], on the other hand, that 'oligaemia in shock is induced by loss of fluid partly into the injured area, partly through the capillaries all over the body' is not borne out by our experiments.

The time limitation of increased permeation in the region adjacent to the trauma, and probably also at the site of the trauma, may have a practical significance for the treatment of cases of traumatic shock. Any therapeutic action intended to arrest the outflow of plasma from the circulation ought to be done

within the first 3–5 hr. after the trauma, since after that time the natural development tends to arrest this condition without outside interference. This conclusion bears out the experience of Slome & O'Shaughnessy [1938] that 'the subject of severe trauma who does not show some sign of recovery under established modes of treatment within two or three hours of his injury is almost inevitably doomed'. The sealing up of the portals from the blood vessels to the tissues may be of mixed benefit, since it does not only stop the outflow of plasma into the tissue, but renders also the reflow into the reversed direction more difficult. This is probably one of the reasons why shock, after having reached a certain stage, is an irreversible condition.

It might be argued that the knee cavity with its synovial membrane is not a true representative of the limb tissue and that the observed changes in dye excretion, as a result of changes in permeability, do not necessitate corresponding changes of permeability in other vessels of the limb. Since the joint cavity, however, is embryologically a natural slit in the limb, and the synovial membrane a derivate of conjunctive tissue, since further its blood supply and innervation are closely related to those of its surroundings, it appears reasonable to assume that it participates equally in all physiological and pathological processes.

Summary

1. When the hind leg of a cat is crushed below the knee and dye (acid fuchsin) injected intravenously, its excretion from the perfused cavity of the knee joint of the same leg increases during the first 1–5 hr. and decreases afterwards. These results suggest an initial increase followed by a late decrease in filtration through the capillaries in tissue adjacent to the trauma. An increased rate of filtration under conditions otherwise unchanged would indicate an increased permeability of the capillaries.

2. There is no corresponding increase in dye excretion from the perfused knee joint when the crushing is inflicted on the forelegs. In this condition the dye excretion decreases during the first 3 hr., probably as a result of a fall in dye concentration in the blood, caused by loss of dye into the traumatized tissue of the forelegs.

3. These results support the view that in 'traumatic shock' increased filtration through the capillaries does not occur throughout the body, but is restricted to the tissue in the neighbourhood of the injury; it occurs there only during the first few hours after the trauma.

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